# Memorandum

To: Interested Parties Date: February 1, 2002

From: Board of Pharmacy

Subject: Informational Hearing

Enclosed is a draft version of guidelines for compounding sterile drug products in a pharmacy. The board plans to hold an informational hearing on these draft guidelines at its April 24-25, 2002 board meeting in Sacramento. The board meeting will be held at:

Department of Consumer Affairs
400 R Street, First Floor Hearing Room
Sacramento, CA 95814

The board welcomes any written comments on the draft guidelines. Please send written comments by the close of business on April 1, 2002 to:

Board of Pharmacy
400 R Street, Suite 4070
Sacramento, CA 95814
Attn: Paul Riches

Written comments may also be submitted by email to Paul_Riches@dca.ca.gov or faxed to (916) 327-6308 by the same deadline. Please include your name and mailing address in your email or fax so that your comments may be properly attributed and so that the board may contact you regarding future actions on the guidelines.

Enclosure

These guidelines are applicable to pharmaceutical services in various practice settings, including, but not limited to, hospitals, community pharmacies, nursing homes, ambulatory care infusion centers, and home care organizations. These guidelines do not apply to the manufacture of sterile pharmaceuticals as defined in state and federal laws and regulations, nor do they apply to the preparation of medications by nurses, physicians or other appropriately licensed health care providers for administration to patients.

Pharmacists are urged to use professional judgment in interpreting these guidelines and applying them in practice. It is recognized that, in emergency situations, a pharmacist may be requested to compound products under conditions that do not meet these guidelines. In such situations, it is incumbent upon the pharmacist to employ professional judgment in weighing the potential patient risks and benefits associated with the compounding procedure in question.

Objectives. The objectives of these guidelines are to provide:

1. Information on quality assurance and quality control activities that must be applied to the preparation of sterile products in pharmacies and
2. A method to match quality assurance and quality control activities with the potential risks to patients posed by various types of products.

## Role of the Pharmacist in Sterile Compounding

*Pharmacist's Responsibility*

A pharmacist dispensing a sterile drug product is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed, and distributed properly. This includes the responsibility for ensuring that the sterile drug product is kept under appropriate controlled conditions at the location of use and that it is administered properly through adequate labeling and verbal or written instructions.

*Quality Assurance*

The dispensing pharmacist is also responsible for ensuring that the sterile drug product retains its quality attributes within acceptable limits through a written quality assurance program. This program should ensure that for the entire labeled life of the product, or until manipulated by the patient or caregiver, the potency, pH, sterility, freedom from pyrogens, particulate limits, container integrity, appearance, and other qualities or characteristics that the sterile drug product is expected to have do exist. The quality assurance program should encompass every sterile drug product under the pharmacy's control and includes all phases of its preparation, distribution, storage, administration, and use. The dispensing pharmacy should employ proper analytical testing, where appropriate, to ensure the microbiological, chemical, and physical quality of all sterile drug products.

The pharmacist is responsible for ensuring that quality is built into the preparation of products, with key factors including at least the following general principles:

1. Personnel are capable and qualified to perform their assigned duties.
2. Ingredients used in compounding have their expected identity, quality, and purity.
3. Critical processes are validated to ensure that procedures, when used, will consistently result in the expected qualities in the finished product.
4. The production environment is suitable for its intended purpose (addressing such matters as environmental cleanliness, control, monitoring, staff attire, and the setting of action limits, as appropriate).
5. Appropriate release checks or testing procedures are performed to ensure that finished products have their expected potency, purity, quality and characteristics at least until the labeled expiration date.
6. Appropriate stability evaluation is performed or determined from the literature for establishing reliable expiration dating to ensure that finished products have the expected potency, purity , quality and characteristics at least until the labeled expiration date.
7. There is assurance that processes are always carried out as intended or specified and are under control.
8. Preparation conditions and procedures are adequate for preventing mix-ups.
9. There are adequate procedures and records for investigating and correcting failures or problems in preparation, testing, or in the product itself.
10. There is adequate separation of quality control functions and decisions from those of production.

**Category 1.**

Category 1 applies to compounded sterile products that exhibit characteristics 1, 2, and 3, stated below. All Category 1 products must be prepared with sterile equipment (e.g., syringes and vials), sterile ingredients and solutions, and sterile contact surfaces for the final product. This category includes compounding which involves only basic, and relatively few, aseptic manipulations that are promptly executed. Category 1 includes the following:

1. Products
    A. Stored at room temperature and completely administered within 28 hours after preparation; or,
    B. Stored under refrigeration for 7 days or less before complete administration to a patient over a period not to exceed 24 hours; or,
    C. Frozen for 30 days or less before complete administration to a patient over a period not to exceed 24 hours.
2. Unpreserved sterile products prepared for administration to one patient or batch-prepared products containing suitable preservatives prepared for administration to more than one patient.
3. Finished products are compounded with commercially available, sterile drug products.

Examples of category 1 processes include transferring a sterile drug product from a vial into a commercially produced i.v. bag; compounding total parenteral nutrient (TPN) solutions by combining dextrose injection and amino acids injection via gravity transfer into a sterile empty container, with or without the subsequent addition of sterile drug products to the final container with a sterile needle and syringe; and transferring a sterile, preserved drug product into sterile syringes with the aid of a mechanical pump and appropriate sterile transfer tubing device.

**Category 2.**

All Category 2 products must be prepared with sterile equipment, sterile ingredients and solutions, and sterile contact surfaces for the final product and with closed system transfer methods. Category 2 sterile products exhibit any of the following characteristics.

1. Products stored beyond 7 days under refrigeration, stored beyond 30 days frozen, or administered beyond 28 hours after preparation and storage at room temperature.
2. Batch-prepared products without preservatives (e.g., epidural products) that are intended for use by more than one patient.
3. Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer; for example, TPN solutions prepared with an automated compounder.
4. Intermediate closed system pooling of sterile drug products
5. Complex or numerous aseptic manipulations executed over a long period

Examples of Category 2 processes include:

Subdividing the contents of a bulk, sterile injectable (without preservatives) into single-dose syringes; and
Compounding TPN solutions with an automated compounding device
Compounding individual finished products for administration as a multi-day infusion via a portable pump or reservoir.

**Category 3.**

Category 3 products exhibit either characteristic 1 or 2:

1. Products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment before terminal sterilization.

2. Products prepared by combining multiple ingredients—sterile or nonsterile —by using an open-system transfer or open reservoir before terminal sterilization. Examples of Category 3 products are calcium levulinate injection, estradiol in oil injection, and morphine sulfate 50-mg/mL injection.

**REQUIREMENTS FOR CATEGORY 1 COMPOUNDING.**

**1.1: Policies and procedures.** Current policies and procedures for compounding sterile products must be in written form and available to all personnel involved in these activities. Before compounding sterile products, all personnel involved must read the policies and procedures. Additions, revisions, and deletions must be communicated to all personnel involved in sterile compounding and related activities. These policies and procedures must address at least the following:

a. Personnel education and training requirements.
b. Competency evaluation.
c. Product acquisition.

d. Storage and handling of products and supplies.
e. Storage and delivery of final products.
f. Use and maintenance of facilities and equipment.
g. Appropriate garb and conduct for personnel working in the controlled area.
h. Process validation.
i. Preparation technique.
j. Labeling.
k. Documentation.
l. Quality control.
m. Personnel access and movement of materials into and near the controlled area.
n. Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations).

Policies and procedures for monitoring environmental conditions in the controlled area must take into consideration the amount of exposure of the product to the environment during compounding and the environmental control devices used to create the critical area.

**1.2: Training & Evaluation.**

The pharmacy must follow a written program of training and performance evaluation designed to ensure that each person working in the aseptic area has the appropriate knowledge and skills necessary to perform the assigned tasks properly. Each person assigned to the aseptic area must successfully complete specialized training in aseptic technique and aseptic area practices.

Training must include didactic material and practical skills activities. Evaluation must include written testing and a written protocol of frequent routine performance checks involving random direct observation of critical operations and adherence to all aseptic area procedures and codes. These the results of these random checks must be documented in the pharmacy. Prompt appropriate action must occur to correct performance deviations, whether detected during performance check or informally. At six-month intervals, each person's continuing training needs must be reassessed, then documented, to ensure that skill levels are maintained.

Training must address at least the following:

a. Aseptic technique
b. Critical-area contamination factors
c. Environmental monitoring
d. Facilities, equipment, and supplies
e. Sterile product calculations and terminology
f. Sterile product compounding documentation
g. Quality assurance procedures
h. Aseptic preparation procedures
i. Proper gowning and gloving technique
j. General conduct in the controlled area.

In addition to knowledge of chemical, pharmaceutical, and clinical properties of drugs, pharmacists must be knowledgeable about the principles of pharmacy compounding. All pharmacy and nonpharmacy personnel (e.g., environmental services staff) who work in the

controlled area must receive documented training on cleaning, sanitizing, and maintaining equipment used in the controlled area.

Training must be specific to the environmental control device and equipment present in the controlled area and must be based on current procedures. The aseptic technique of each person preparing sterile products must be observed and evaluated as satisfactory during orientation and training and at least every six months thereafter.

### 1.3: Ingredient Storage & Handling

Solutions, drugs, supplies, and equipment used to prepare or administer sterile products must be stored in accordance with manufacturer or USP requirements.
Temperatures in refrigerators and freezers used to store ingredients and finished sterile preparations must be monitored and documented daily to ensure that compendial storage requirements are met.
Warehouse and other pharmacy storage areas where ingredients are stored must be monitored to ensure that temperature, light, moisture, and ventilation remain within manufacturer and compendial requirements.

1. To permit adequate floor cleaning, drugs, supplies, and compounding equipment must be stored on shelving, cabinets, and carts above the floor.
2. Products that have exceeded their expiration dates must be removed from active storage areas.
3. Before use, each drug, ingredient, and container must be visually inspected for damage, defects, and expiration date.
4. Unnecessary personnel traffic in the controlled area must be minimized.
5. Particle-generating activities, such as removal of intravenous solutions, drugs, and supplies from cardboard boxes, must not be performed in the controlled area.
6. Products and supplies used in preparing sterile products must be removed from shipping containers outside the controlled area before aseptic processing is begun.
7. Packaging materials and items generating unacceptable amounts of particles (e.g., cardboard boxes, paper towels [unless lint-free], reference books) must not be permitted in the controlled area or critical area. The removal of immediate packaging designed to retain the sterility or stability of a product is an exception; obviously, this type of packaging must not be removed outside the controlled area.
8. Disposal of packaging materials, used syringes, containers, and needles must be performed at least daily, and more often if needed, to enhance sanitation and avoid accumulation in the controlled area.
9. Trash cans must be below the level of the laminar-airflow workbench and must be removed from the controlled area before being emptied.
10. Sharps containers must be safely placed into the waste stream, according to policies developed by the pharmacy to comply with regulations of the Occupational Safety and Health Administration (OSHA).

In the event of a product recall, there must be a  mechanism for tracking and retrieving affected products from specific patients to whom the products were dispensed.

### 1.4: Facilities & Equipment.

The controlled area must be a limited-access area sufficiently separated from other pharmacy operations to minimize the potential for contamination that could result from the unnecessary flow of materials and personnel into and out of the area. The controlled area is a buffer from outside air that is needed because strong air currents from briefly opened doors, personnel walking past the laminar-airflow workbench, or the air stream from the heating, ventilating, and air conditioning system can easily exceed the velocity of air from the laminar-airflow workbench. Also, operators introducing supplies into the laminar-airflow workbench or reaching in with their arms can drag contaminants from the environment surrounding the workbench.

Cleanliness of the controlled area can be enhanced by:

a. Limiting access to those personnel assigned to work in the controlled area
b. Having those personnel wear the appropriate garb
c. donning and removing garb outside the controlled area
d. keeping doors to the controlled area closed
e. limiting storage in the controlled area to items in constant use
f. using low-particulate shelving, counters, and carts in the controlled area
g. not allowing cardboard and other particle-generating materials in the controlled area
h. controlling the temperature and humidity inside the room
i. implementing a regular cleaning and maintenance schedule

Barrier isolator workstations are closed systems and are not as sensitive to their external environment as laminar-airflow equipment. It is good practice to (1) place barrier isolator workstations in limited-access areas, (2) control the temperature and humidity of the surrounding area, and (3) clean and sanitize the surrounding area on a routine basis. Special precautions must be taken to clean equipment and compounding areas meticulously after preparing products that contain allergenic ingredients.

Computer entry, order processing, label generation, and record keeping must be performed outside the critical area. The controlled area must be well organized and lighted and of sufficient size to support sterile compounding activities. For hand washing, a sink with hot and cold running water must be in close proximity to but outside the controlled area. Refrigeration, freezing, ventilation, and room temperature control capabilities appropriate for storage of ingredients, supplies, and pharmacy-prepared sterile products in accordance with manufacturer, USP, and state or federal requirements must exist. The controlled area must be cleaned and disinfected at regular intervals with appropriate agents, according to written policies and procedures. Disinfectants must be alternated periodically to prevent development of resistant microorganisms.

The floors of the controlled area must be nonporous and washable to enable regular disinfection. Active work surfaces in the controlled area must be disinfected, in accordance with written procedures. Refrigerators, freezers, shelves, and other areas where pharmacy-prepared sterile products are stored must be kept clean.

Cytotoxic and other hazardous products must be prepared in a vented class II biological safety cabinet or a barrier isolator of appropriate design to meet the personnel exposure limits described in product material safety data sheets. Properly maintained barrier isolators provide suitable environments for the preparation of Category 1, 2, and 3 sterile products.

Laminar-airflow workbenches are designed to be operated continuously. If a laminar-airflow workbench is turned off between aseptic processes, it must be operated long enough to allow complete purging of room air from the critical area then disinfected before use. Barrier isolators, because of their closed nature, require less start-up time. If the barrier isolator has been turned off for less than 24 hours, a two-minute start-up time is sufficient. For periods greater than 24 hours, the chamber must be sanitized and the isolator must not be used for a minimum of 10 minutes after application of the sanitizing agent. The critical-area work surface and all accessible interior surfaces of the workbench must be disinfected with an appropriate agent before work begins and periodically thereafter, in accordance with written policies and procedures. The exterior surfaces of the laminar-airflow workbench must be cleaned periodically with a mild detergent or suitable disinfectant.

The laminar-airflow workbench must be certified by a qualified contractor every six months or when it is relocated to ensure operational efficiency and integrity. Prefilters in the laminar-airflow workbench must be changed (or cleaned, if they are washable) periodically, in accordance with written policies and procedures. A method must be established for calibrating and verifying the accuracy of automated compounding devices used in aseptic processing.

**1.5: Garb.**

Procedures must require that personnel wear clean gowns or coveralls that generate few particles in the controlled area. Scrub attire by itself is not acceptable (but can, like street clothes, be covered by a gown or coverall). Hand, finger, and wrist jewelry must be minimized or eliminated. Fingernails must be kept clean and trimmed. Head and facial hair must be covered. Masks are recommended because most personnel talk or may cough or sneeze. Gloves are recommended.

**1.6: Aseptic Technique & Product Preparation.**

Sterile products must be prepared with aseptic technique in a class 100 environment. Personnel must scrub their hands and forearms for an appropriate length of time with a suitable antimicrobial skin cleanser at the beginning of each aseptic compounding process and when reentering the controlled area, in accordance with written procedures. Eating, drinking, and smoking are prohibited in the controlled area. Talking must be minimized in the critical area during aseptic preparation (even when masks are worn). Ingredients used to compound sterile products must be determined to be stable, compatible, and appropriate for the product to be prepared, according to manufacturer or USP guidelines or appropriate scientific references. The ingredients of the preparation must be predetermined to result in a final product that meets physiological norms for solution osmolality and pH, as appropriate for the intended route of administration. Each ingredient and container must be inspected for defects, expiration date, and product integrity before use. Expired, inappropriately stored, or defective products must not be used in preparing sterile products. Only materials essential for preparing the sterile product must be placed in the laminar-airflow workbench or barrier isolator. The surfaces of ampuls, vials, and container closures must be disinfected by swabbing or spraying with an appropriate disinfectant solution before placement in the workbench.

Materials used in aseptic preparation must be arranged in the critical area (within the laminar-airflow workbench or barrier isolator) in a manner that prevents interruption of the unidirectional airflow between the high-efficiency particulate air (HEPA) filter and critical sites of needles,

vials, ampuls, containers, and transfer sets. All aseptic procedures must be performed at least 6 inches inside the front edge of the laminar-airflow workbench, in a clear path of unidirectional airflow between the HEPA filter and work materials (e.g., needles, closures). The number of personnel preparing sterile products in the workbench at one time must be minimized. Overcrowding of the critical work area may interfere with unidirectional airflow and increase the potential for compounding errors. Likewise, the number of units being prepared in the workbench at one time must allow unobstructed airflow over critical areas. Automated compounding devices and other equipment placed in or adjacent to the critical area must be cleaned, disinfected, and placed to avoid contamination or disruption of the unidirectional airflow between the HEPA filter and sterile surfaces. Closed systems like barrier isolators require less stringent placement of sterile units and equipment because the critical area encompasses the entire work surface. Hand and arm movements are not critical because the walls of the barrier isolator provide protection from the outside environment.

Aseptic technique must be used to avoid touch contamination of sterile needles, syringe parts, and other critical sites. Solutions from ampuls must be properly filtered to remove particles. Solutions of reconstituted powders must be mixed carefully, ensuring complete dissolution of the drug with the appropriate diluent. Some patients may require a latex-free admixture to avoid severe allergic reactions. Latex-related policies and procedures must be developed by each institution, given the paucity of evidence that latex closures and syringe plungers are implicated in patient reactions to latex. Before, during, and after the preparation of sterile products, the pharmacist must carefully check the identity and verify the amounts and sequence of the additives in sterile preparations against the original prescription, medication order, or other appropriate documentation before the product is released or dispensed.

**1.7: Process validation.**

Validation of aseptic processing procedures provides a mechanism for ensuring that processes consistently result in sterile products of acceptable quality. In Category 1, process validation (or process simulation) of compounding procedures is actually method of assessing the adequacy of an operator's aseptic technique. Each individual involved in the preparation of sterile products must successfully complete a validation process on technique before being allowed to prepare sterile products. The validation process must follow written procedures. Process simulation allows for the evaluation of opportunities for microbial contamination during all steps of sterile product preparation. The sterility of the final product is a cumulative function of all processes involved in its preparation and is ultimately determined by the processing step providing the lowest probability of sterility. Process simulation testing is carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The same personnel, procedures, equipment, and materials are involved. Completed medium samples are incubated. If no microbial growth is detected, this provides evidence that adequate aseptic technique was used. If growth is detected, the entire sterile preparation process must be evaluated, corrective action taken, and the process simulation test performed again. No products intended for patient use must be prepared by an individual until the process simulation test indicates that the individual can competently perform aseptic procedures. It is recommended that personnel competency be revalidated at least every six months, whenever the quality assurance program yields an unacceptable result, and whenever unacceptable techniques are observed; this revalidation must be documented.

**1.8: Expiration dating.**

All pharmacy-prepared sterile products must bear an appropriate expiration date. The expiration date assigned must be based on currently available drug stability information and sterility considerations. Sources of drug stability information include references (e.g., AHFS Drug Information, Extended Stability for Parenteral Drugs, Handbook on Injectable Drugs, King Guide to Parenteral Admixtures), manufacturer recommendations, and reliable, published research. When interpreting published drug stability information, the pharmacist must consider all aspects of the final sterile product being prepared (e.g., drug reservoir, drug concentration, storage conditions).

Methods used for establishing expiration dates must be documented. Appropriate inhouse (or contract service) stability testing may be used to determine expiration dates when drug stability data are not readily available. Home care pharmacies are often required to assign extended beyond- use dates to sterile products, so ASHP has published guidelines for home care pharmacies that address beyond-use dating.

**1.9: Labeling.**

Sterile products must be labeled in accordance with Section 4076 of the Business and Professions Code. In addition, the label on sterile drug products must include:

The pharmacy's telephone number.
The names and concentrations of all ingredients in the sterile drug product.
The labels on cytotoxic agents must include the following warning, "Chemotherapy – Dispose of Properly."

The label must be legible and affixed to the final container in a manner enabling it to be read while the sterile product is being administered (when possible).

**1.10: End-product evaluation.**

The final product must be inspected when preparation is completed and again when the product is dispensed. This inspection includes an evaluation for container leaks, container integrity, solution cloudiness or phase separation, particulates in the solution, appropriate solution color, and solution volume. The responsible pharmacist must verify that the product was compounded accurately with the correct ingredients, quantities of each ingredient, containers, and reservoirs; different methods may be used for end-product verification (e.g., observation, calculation checks, documented records). Refractive index measurement may also be used to verify the addition of dextrose, for example in parenteral nutrient solutions.

**1.11: Handling of sterile products outside the pharmacy.**

Pharmacists must participate in developing procedures for the safe use of sterile products once they are distributed outside the pharmacy. How the product is transported from the pharmacy, how it is stored outside the pharmacy, and methods for return, recycling, and disposal must be addressed in written policies and procedures. Sterile products must be transported so as to be protected from extremes of temperature outside their range of stability and from light if they are photosensitive. Storage containers and packaging verified as suitable for protection during transport must be specified. Transit time and conditions must also be specified and controlled.

Delivery personnel must be instructed on special handling procedures. Special instructions for storage must be a part of the label or a separate information sheet.

**1.12: Documentation.**

The following must be documented and maintained on file for an adequate period of time, according to organizational policies and state regulatory requirements:

(1) the training and competency evaluation of employees in sterile product procedures,
(2) refrigerator and freezer temperatures,
(3) certification of laminar-airflow workbenches, and
(4) other facility quality control logs specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment).

**Quality assurance for Category 2**

Because the risks of inaccurate products are associated with more complex procedures and because instability and contamination are more likely with long-term storage and administration, more stringent requirements are appropriate for Category 2 preparations. These requirements may be viewed as more important in circumstances where the medical need is routine. In circumstances where the medical need for a product is immediate (and there is not a suitable alternative) or when the preparation of such a product is rare, professional judgment must be applied to the extent to which some guidelines (e.g., cleanroom design and final product testing before product dispensing) must be applied.

**REQUIREMENTS FOR CATEGORY II COMPOUNDING.**

**2.1: Policies and procedures.** In addition to all guidelines for Category 1, a written quality assurance program must define and identify necessary environmental monitoring devices and techniques to be used to ensure an adequate environment for Category 2 sterile product preparation. Examples include the use of airborne particle counters, air velocity and temperature meters, viable particle samplers, agar plates, and swab sampling of surfaces and potential contamination sites. All aspects of Category 2 sterile product preparation, storage, and distribution, including such details as the choice of cleaning materials and disinfectants and the monitoring of equipment accuracy, must be addressed in written policies and procedures. Limits of acceptability (threshold or action levels) for environmental monitoring and process validation and actions to be implemented when thresholds are exceeded must be defined in written policies. For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets and for appropriate documentation. Policies and procedures must also address personnel attire in the controlled area, lot number determination and documentation, and any other quality assurance procedures unique to compounding Category 2 sterile products.

**2.2: Personnel education, training, and evaluation**. All guidelines for Category 1 must be met. In addition to guidelines for Category 1, assessment of the competency of personnel preparing Category 2 sterile products must include appropriate process validation. However, process simulation procedures for assessing the preparation of Category 2 sterile products must be representative of all types of manipulations, products, and batch sizes personnel preparing

Category 2 products are likely to encounter. Personnel must also be taught which products are to undergo end-product quantitative analysis.

**2.3: Storage and handling.** All storage and handling guidelines for Category 1 must be met.

**2.4: Facilities and equipment.** In addition to all guidelines for Category 1, the following guidelines must be followed for Category 2 sterile product preparation:

1. The controlled area must meet the standards of a class 10,000 cleanroom, as defined by Federal Standard 209E.85. A positive air pressure relative to adjacent pharmacy areas is required, as are an appropriate number of air exchanges per hour and appropriate humidity and temperature levels. For open-architecture cleanrooms, it is appropriate to measure the volume of air entering the cleanroom versus the volume of air entering adjacent rooms, so as to ensure a positive pressure gradient for the cleanroom. To allow proper cleaning and disinfection, walls, floors, and ceilings in the controlled area must be nonporous. To help reduce the number of particles in the controlled area, an adjacent support area must be provided. A properly maintained barrier isolator also provides an acceptable environment. A barrier isolator provides a class 100 environment for product preparation; therefore, the isolator itself can be in a separate area of the pharmacy but need not actually be in a cleanroom.

2. Cleaning materials (e.g., mops, sponges, and germicidal disinfectants) for use in the cleanroom must be carefully selected. They must be made of materials that generate a low amount of particles. If reused, cleaning materials must be cleaned and disinfected between uses.

3. The critical-area work surfaces must be disinfected frequently and before and after each batch-preparation process with an appropriate agent, according to written policies and procedures. Floors must be disinfected at least daily. Carpet or porous floors, porous walls, and porous ceiling tiles are not suitable in the controlled area because these surfaces cannot be properly cleaned and disinfected. Exterior workbench surfaces and other hard surfaces in the controlled area, such as shelves, carts, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Walls must be cleaned at least monthly.

4. To help reduce the number of particles in the controlled area, an adjacent support area (e.g., anteroom) of high cleanliness, separated from the controlled area by a barrier (e.g., plastic curtain, partition, wall), is recommended. Appropriate activities for the support area include, but are not limited to, hand washing, gowning and gloving, removal of packaging and cardboard items, and cleaning and disinfecting hard-surface containers and supplies before placing these items into the controlled area.

5. Methods must be established for calibrating and verifying the accuracy and sterility of automated compounding methods used in aseptic processing.

**2.5: Garb.** All guidelines for Category 1 must be met. Gloves, gowns, and masks are required for the preparation of all Category 2 sterile products. Even when sterile gloves are used, they do not remain sterile during aseptic compounding; however, they do assist in containing bacteria, skin, and other particles that may be shed even from scrubbed hands. Clean gowns, coveralls, or

closed jackets with sleeves having elastic binding at the cuff are recommended; these garments must be made of low-shedding materials. Shoe covers may be helpful in maintaining the cleanliness of the controlled area.

Barrier isolators do not require the same level of gowning as laminar-airflow workstations as long as they operate as closed systems with HEPA filtration of air entering and leaving the barrier isolator and a separate area for entrance, such as an air lock for product transfers.

During sterile product preparation, gloves must be rinsed frequently with a suitable agent and changed when their integrity is compromised. Personnel must discard gloves upon leaving the cleanroom and don new gloves upon reentering the cleanroom.

**2.6: Aseptic technique and product preparation.** All guidelines for Category 1 sterile product preparation must be met. Relative to batch-prepared products, a master work sheet must be developed for a batch of each discrete identity and concentration of sterile product to be prepared. The master work sheet must consist of the formula, components, compounding directions or procedures, a sample label, and evaluation and testing requirements. Once the original master work sheet is approved by the designated pharmacist, a verified duplicate (e.g., a photocopy) of the master work sheet must be used as the preparation work sheet from which each batch is prepared and on which all documentation for each batch occurs. (For small-formula, frequently prepared batches, it may be more efficient to have multiple lines on the preparation work sheet for documenting more than one batch.) The preparation work sheet must be used to document the following:

1. Identity of all solutions and ingredients and their corresponding amounts, concentrations, or volumes,
2. Manufacturer lot number and expiration date for each component,
3. Component manufacturer or suitable manufacturer identification number,
4. Container specifications (e.g., syringe, pump cassette),
5. Lot or control number assigned to batch,
6. Expiration date of batch-prepared products,
7. Date of preparation,
8. Identity (e.g., initials, codes, signatures) of personnel involved in preparation,
9. End-product evaluation and testing specifications and results,
10. Storage requirements,
11. Specific equipment used during aseptic preparation (e.g., a specific automated compounding device), and
12. Comparison of actual yield with anticipated yield, when appropriate.

However documentation is done, a procedure must exist for easy retrieval of all records pertaining to a particular batch. Each batch of sterile products must bear a unique lot number. Identical lot numbers must never be assigned to different products or different batches of the same product. Lot numbers may be alphabetic, numeric, or alphanumeric. The process of combining multiple sterile ingredients into a single sterile reservoir for subdivision into multiple units for dispensing may necessitate additional quality control procedures. A second pharmacist must verify calculations associated with this process, when possible; this verification must be documented. Because this process often involves making multiple entries into the intermediate sterile reservoir, the likelihood of contamination may be greater than that associated with the preparation of other Category 2 sterile products. For preparation involving automated

compounding devices, a pharmacist must verify data entered into the compounding device before compounding begins. End-product checks must be performed to verify accuracy of ingredient delivery. The operator must also periodically observe the device during the mixing process to ensure that the device is operating properly. If there are doubts whether a product or component has been properly prepared or stored, the product must not be used.

**2.7: Process validation.** Each individual involved in the preparation of Category 2 sterile products must successfully complete a validation process, as recommended for Category 1. Process simulation for compounding Category 2 sterile products must be representative of all types of manipulations, products, and batch sizes that personnel preparing Category 2 sterile products are likely to encounter.

**2.8: Expiration dating.** All guidelines for Category 1 must be met.

**2.9: Labeling.** All guidelines for Category 1 must be met.

**2.10: End-product evaluation.** All guidelines for Category 1 must be met. For complex or toxic products, it is appropriate, when possible, to obtain quantitative testing of the accuracy of sterile additives.

**2.11: Handling of sterile products outside the pharmacy.** All guidelines for Category 1 must be met.

**2.12: Documentation.** All guidelines for Category 1 must be met. Additionally, documentation of end-product sampling and batch preparation records must be maintained for an three years. Documentation for sterile batch-prepared products must include the

1. Master work sheet,
2. Preparation work sheet, and
3. End-product evaluation and testing results.

**QUALITY ASSURANCE FOR CATEGORY 3.**

Category 3 addresses the preparation of products that pose the greatest potential risk to patients. The quality assurance activities described in this section are clearly more demanding —in terms of processes, facilities, and final product assessment —than for Categories 1 and 2.
Ideally, the activities described for Category 3 would be used for all high-risk products. However, the activities may be viewed as most important in circumstances where the medical need for such high-risk products is routine. In circumstances where the medical need for such a product is immediate (and there is not a suitable alternative) or when the preparation of such a product is rare, professional judgment must be applied as to the extent to which some activities must be applied.

**3.1: Policies and procedures.** There must be written policies and procedures related to every aspect of preparation of Category 3 sterile products. These policies and procedures must be detailed enough to ensure that all products have the identity, strength, quality, and purity purported for the product. All policies and procedures must be reviewed and approved by the designated pharmacist. There must be a mechanism designed to ensure that policies and procedures are communicated, understood, and adhered to by personnel cleaning or working in

the controlled area or support area. Written policies and procedures must define and identify the environmental monitoring activities necessary to ensure an adequate environment for Category 3 sterile product preparation. In addition to the policies and procedures required for Categories 1 and 2, there must be written policies and procedures for the following:

1. Component selection, handling, and storage,
2. Any additional personnel qualifications commensurate with the preparation of Category 3 sterile products,
3. Personnel responsibilities in the controlled area
4. Equipment use, maintenance, calibration, and testing,
5. Sterilization and expiration dating,
6. Master formula and master work sheet development and use,
7. End-product evaluation and testing,
8. Appropriate documentation for preparation of Category 3 sterile products,
9. Use, control, and monitoring of environmentally controlled areas and calibration of monitoring equipment,
10. Process simulation for each Category 3 sterile product,
11. Quarantine of products and release from quarantine, if applicable,
12. A mechanism for recalling products from patients in the event that end product testing procedures yield unacceptable results, and
13. Any other quality control procedures unique to the preparation of Category 3 sterile products.

**3.2: Personnel education, training, and evaluation.** Persons preparing sterile products at Category 3 must have specific education, training, and experience to perform all functions required for the preparation of Category 3 sterile products. However, final responsibility must lie with the pharmacist, who must be knowledgeable in pharmacy compounding practice and proficient in quality assurance requirements, equipment used in the preparation of Category 3 sterile products, and other aspects of sterile product preparation. The pharmacist must have sufficient education, training, experience, and demonstrated competency to ensure that all sterile products prepared from sterile or nonsterile components have the identity, strength, quality, and purity purported for the products. In addition to the body of knowledge required for Categories 1 and 2, the pharmacist must possess sufficient knowledge in the following areas:

1. Aseptic processing,
2. Quality control and quality assurance as related to environmental, component, and end-product testing,
3. Sterilization techniques, and
4. Container, equipment, and closure system selection.

All pharmacy personnel involved in the cleaning and maintenance of the controlled area must be specially trained and thoroughly knowledgeable in the special requirements of class 100 critical-area technology and design. There must be documented, ongoing training for all employees to enable retention of expertise.

**3.3: Storage and handling.** In addition to guidelines for Categories 1 and 2, Category 3 policies and procedures for storage and handling must include procurement, identification, storage, handling, testing, and recall of nonsterile components.

Components and finished products ready to undergo end-product testing must be stored in a manner that prevents their use before release by a pharmacist, minimizes the risk of contamination, and enables identification. There must be identified storage areas that can be used to quarantine products, if necessary, before they are released.

**3.4: Facilities and equipment.** Preparation of Category 3 sterile products must occur in a class 100 horizontal- or vertical-laminar-airflow workbench that is properly situated in a class 10,000 cleanroom or in a properly maintained and monitored class 100 cleanroom (without the workbench). The cleanroom area must have a positive pressure differential relative to adjacent, less clean areas of at least 0.05 inch of water. A properly designed and maintained barrier isolator provides an aseptic environment for Category 3 products. To allow proper cleaning and disinfection, walls, floors, and ceilings in the controlled area must be nonporous. To help reduce the number of particles in the controlled area, an adjacent support area (e.g., ante- room) must be provided. During the preparation of Category 3 sterile products, access to the controlled area or cleanroom must be limited to those individuals who are required to be in the area and are properly attired. The environment of the main access areas directly adjacent to the controlled area (e.g., anteroom) must meet at least Federal Standard 209E class 100,000 requirements. To help maintain a class 100 critical-area environment during compounding, the adjacent support area (e.g., anteroom) must be separated from the controlled area by a barrier (e.g., plastic curtain, partition, wall). Written policies and procedures for monitoring the environment of the controlled area and adjacent areas must be developed. No sterile products must be prepared in the controlled area if it fails to meet established criteria specified in the policies and procedures. A calibrated particle counter capable of measuring air particles 0.5 mm and larger must be used to monitor airborne particulate matter. Before product preparation begins, the positive- pressure air status must meet or exceed the requirements. Air samples must be taken at several places in the controlled area with the appropriate environmental monitoring devices (e.g., nutrient agar plates). Surfaces on which work actually occurs, including laminar-airflow workbench surfaces and tabletops, must be monitored by using surface contact plates, the swab-rinse technique, or other appropriate methods. Test results must be reviewed and criteria must be preestablished to determine the point at which the preparation of Category 3 sterile products will be disallowed until corrective measures are taken. When the environment does not meet the criteria specified in the policies and procedures, sterile product processing must immediately cease and corrective action must be taken. In the event that this occurs, written policies and procedures must delineate alternative methods of sterile product preparation to enable timely fulfillment of prescription orders. Equipment must be adequate to prevent microbiological contamination. Methods must be established for the cleaning, preparation, sterilization, calibration, and documented use of all equipment. Critical-area work surfaces must be disinfected with an appropriate agent before the preparation of each product. Floors in the controlled area must be disinfected at least daily. Exterior workbench surfaces and other hard surfaces in the controlled area, such as shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Walls and ceilings in the controlled area or cleanroom must be disinfected at least weekly. Large pieces of equipment, such as tanks, carts, and tables, used in the controlled area or cleanroom must be made of a material that can be easily cleaned and disinfected; stainless steel is recommended. Stools and chairs must be cleanroom quality. Equipment that does not come in direct contact with the finished product must be properly cleaned, rinsed, and disinfected before being placed in the controlled area. All nonsterile equipment that will come in contact with the sterilized final product must be properly sterilized before introduction into the controlled area; this precaution includes such items as tubing, filters,

containers, and other processing equipment. The sterilization process must be monitored and documented.

**3.5: Garb.** All guidelines for Categories 1 and 2 must be met. Additionally, cleanroom garb must be worn inside the controlled area at all times during the preparation of Category 3 sterile products. Attire must consist of a low-shedding coverall, head cover, face mask, and shoe covers. These garments may be either disposable or reusable. Head and facial hair must be covered. Before donning these garments over street clothes, personnel must thoroughly wash their hands and forearms with a suitable antimicrobial skin cleanser. Sterile disposable gloves must be worn and rinsed frequently with an appropriate agent (e.g., 70% isopropyl alcohol) during processing. The gloves must be changed if their integrity is compromised. If persons leave the controlled area or support area during processing, they must regown with clean garments before reentering.

**3.6: Aseptic technique and product preparation.** All guidelines for Categories 1 and 2 must be met. Methods must ensure that components and containers remain free from contamination and are easily identified as to the product, lot number, and expiration date. If components are not finished sterile pharmaceuticals obtained from licensed manufacturers, pharmacists must ensure that these components meet USP and FDA standards. Products prepared from nonsterile ingredients must be tested to ensure that they do not exceed specified endotoxin limits, unless the ingredient will denature all proteins. As each new lot of components and containers is received, the components must be quarantined until properly identified, tested, or verified by a pharmacist.

The methods for preparing sterile products and using process controls must be designed to ensure that finished products have the identity, strength, quality, and purity they are intended to have. Any deviations from established methods must be documented and appropriately justified. A master work sheet must be developed for the preparation of each Category 3 sterile product. Once the pharmacist approves the master work sheet, a verified duplicate of the master work sheet must be used as the controlling document from which each sterile end product or batch of prepared products is compounded and on which all documentation for that product or batch occurs. The preparation work sheet must document all the requirements for Category 2 plus the following:

1. Comparison of actual with anticipated yield,
2. Sterilization methods
3. Pyrogen testing
4. Quarantine specifications.

The preparation work sheet must serve as the batch record for each time a Category 3 sterile product is prepared. Each batch of pharmacy prepared sterile products must bear a unique lot number, as described in Category 2. There must be documentation on the preparation work sheet of all additions of individual components plus the signatures or initials of those individuals involved in the measuring or weighing and addition of these components. The selection of the final packaging system (including container and closure) for the sterile product is crucial to maintaining product integrity. To the extent possible, presterilized containers obtained from licensed manufacturers must be used. If an aseptic filling operation is used, the container must be sterile at the time of the filling operation. If nonsterile containers are used, methods for sterilizing these containers must be established. Final containers selected must be capable of maintaining product integrity throughout the shelf life of the product. For products requiring sterilization, selection of an appropriate method of sterilization is of prime importance. Methods

of product sterilization include sterile filtration, autoclaving, dry heat sterilization, chemical sterilization, and irradiation. The pharmacist must ensure that the sterilization method used is appropriate for the product components and does not alter the pharmaceutical properties of the final product. A method of sterilization often used by pharmacists is sterile filtration. In sterile filtration, the filter must be chosen to fit the chemical nature of the product, and the product must be filtered into presterilized containers under aseptic conditions. Sterilizing filters of 0.22-mm or smaller porosity must be used in this process. Colloidalor viscous products may require a 0.45-mm filter; however, extreme caution must be exercised in these circumstances, and more stringent end-product sterility testing is essential. To ensure that a bacteria-retentive filter did not rupture during filtration of a product, an integrity test must be performed on all filters immediately after filtration. This test may be accomplished by performing a bubble point test, in which pressurized gas is applied to the upstream side of the filter with the downstream outlet immersed in water and the pressure at which a steady stream of bubbles begins to appear is noted. The observed pressure is then compared with the manufacturer's specification for the filter. To compare the used filter with the manufacturer's specifications, which would be based on the filtration of water through the filter, it is necessary to first rinse the filter with sterile water for injection. An observed value lower than the manufacturer's specification indicates that the filter was defective or ruptured during the sterilization process. Methods must be established for handling, testing, and resterilizing any product processed with a filter that fails the integrity test.

**3.7: Process validation.** In addition to Category 1 and 2 guidelines, written policies and procedures must be established to validate all processes involved in the preparation of Category 3 sterile products (including all procedures, equipment, and techniques) from sterile or nonsterile components. In addition to evaluating personnel technique, process validation provides a mechanism for determining whether a particular process will, when performed by qualified personnel, consistently produce the intended results.

**3.8: Expiration dating.** In addition to Categories 2 guidelines, there must be reliable methods for establishing all expiration dates, including laboratory testing of products for sterility, nonpyrogenicity, and chemical content, when necessary. These tests must be conducted in a manner based on appropriate statistical criteria, and the results documented.

**3.9: Labeling.** All guidelines for Categories 1 and 2 must be met.

**3.10: End-product evaluation.** For each preparation of a sterile product or a batch of sterile products, there must be appropriate laboratory determination of conformity to established written specifications and policies. Any reprocessed material must undergo complete final product testing. Additionally, process validation must be supplemented with a program of end-product sterility testing, according to a formal sampling plan. Written policies and procedures must specify measurements and methods of testing. Policies and procedures must include a statistically valid sampling plan and acceptance criteria for the sampling and testing. The criteria must be statistically adequate to reasonably ensure that the entire batch meets all specifications. Products not meeting all specifications must be rejected and discarded. There must be a mechanism for recalling all products of a specific batch if end-product-testing procedures yield unacceptable results. On completion of final testing, products must be stored in a manner that ensures their identity, strength, quality, and purity. It is advisable to quarantine sterile products compounded from nonsterile components, pending the results of end-product testing. If products prepared from nonsterile components must be dispensed before satisfactory completion of end-

product testing, there must be a procedure to allow for immediate recall of the products from patients to whom they were dispensed.

**3.11: Handling of sterile products outside the pharmacy.** All guidelines for Categories 1 and 2 must be met.

**3.12: Documentation.** In addition to the guidelines for Categories 1 and 2, documentation for Category 3 sterile products must include

1. Preparation work sheet,
2. Sterilization records of final products (if applicable),
3. Quarantine records (if applicable), and
4. End-product evaluation and testing results.

## Appendix A—Glossary

**Action level:** Established particulate or microbial counts or results that require corrective action when exceeded.
**Aseptic preparation or aseptic processing:** The technique involving procedures designed to preclude contamination (of drugs, packaging, equipment, or supplies) by microorganisms during processing.
**Batch preparation:** Compounding of multiple sterile product units, in a single discrete process, by the same individuals, carried out during one limited time period.
**Cleanroom:** A room (1) in which the concentration of airborne particles is controlled, (2) that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and (3) in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary. For example, the air particle count in a class 100 cleanroom cannot exceed a total of 100 particles 0.5 mm or larger per cubic foot of air.
**Clean zone:** Dedicated space (1) in which the concentration of airborne particles is controlled, (2) that is constructed and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone, and (3) in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary. This zone may be open or enclosed and may or may not be located within a cleanroom. For example, an open-architecture controlled area should be a clean zone.
**Closed-system transfer:** The movement of sterile products from one container to another in which the containers–closure system and transfer devices remain intact throughout the entire transfer process, compromised only by the penetration of a sterile, pyrogen-free needle or cannula through a designated closure or port to effect transfer, withdrawal, or delivery. Withdrawal of a sterile solution from an ampul through a particulate filter in a class 100 environment would generally be considered acceptable; however, the use of a flexible closure vial, when available, would be preferable.
**Compounding:** For purposes of these guidelines, compounding simply means the mixing of ingredients to prepare a medication for patient use. This activity would include dilution, admixture, repackaging, reconstitution, and other manipulations of sterile products.
**Controlled area:** For purposes of these guidelines, a controlled area is the area designated for preparing sterile products. This is referred to as the buffer zone (i.e., the cleanroom in which the laminar-airflow workbench is located) by USP.
**Corrective action:** Action to be taken when the results of monitoring indicate a loss of control or when action levels are exceeded.
**Critical area:** Any area in the controlled area where products or containers are exposed to the environment.
**Critical site:** An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment.
**Critical surface:** Any surface that comes into contact with previously sterilized products or containers.
**Designated pharmacist:** The pharmacist chosen by experience and training to be in charge of a sterile product preparation area or unit in a licensed pharmacy.
**Expiration date:** The date (and time, when applicable) beyond which a product should not be used (i.e., the product should be discarded beyond this date and time). Expiration date and time should be assigned on the basis of both stability and risk level, whichever is the shorter period. Note: Circumstances may occur in which the expiration date and time arrive while an infusion is in progress. When this occurs, judgment should be applied in determining whether it is

appropriate to discontinue that infusion and replace the product. Organizational policies on this should be clear.

**High-efficiency particulate air (HEPA) filter:** A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove 99.97% of all air particles 0.3 mm or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminarairflow workbench, an environment can be created consistent with standards for a class 100 cleanroom.

**Isolator (or barrier isolator):** A closed system made up of four solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of both inlet and exhaust air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half-suits.

**Media fill:** See process validation or simulation.

**Preservatives:** For purposes of these guidelines, preservatives refer to any additive intended to extend the content, stability, or sterility of active ingredients (e.g., antioxidants, emulsifiers, bacteriocides).

**Process validation or simulation:** Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product and with the same container or closure system.30 Process simulation tests are synonymous with medium fills, simulated product fills, broth trials, and broth fills.

**Quality assurance:** For purposes of these guidelines, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug products lead to products that meet predetermined standards of quality.

**Quality control:** For purposes of these guidelines, quality control is the set of testing activities used to determine that the ingredients, components (e.g., containers), and final sterile products prepared meet predetermined requirements with
respect to identity, purity, nonpyrogenicity, and sterility.

**Repackaging:** The subdivision or transfer of a compounded product from one container or device to a different container or device, such as a syringe or an ophthalmic container.

**Sterilization:** A validated process used to render a product free of viable organisms.

**Sterilizing filter:** A filter that, when challenged with a solution containing the microorganism *Pseudomonas diminuta* at a minimum concentration of 1012 organisms per square centimeter of filter surface, will produce a sterile effluent.

**Temperatures (USP):** Frozen means temperatures between –20 and –10 °C (–4 and 14 °F). Refrigerated means temperatures between 2 and 8 °C (36 and 46 °F). Room temperature means temperatures between 15 and 30 °C (59 and 86 °F).

**Validation:** Documented evidence providing a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

**Worst case:** A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions. Such conditions do not necessarily induce product or process failure.